



N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.

2200 PENNSYLVANIA AVENUE, N.W., SUITE 100W, WASHINGTON, D.C. 20037 • (202) 557-3800 • FAX (202) 557-3836

MANAGED BY B&C CONSORTIA MANAGEMENT, L.L.C.

August 16, 2018

Via Docket Submission

Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPT)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460-0001

Re: Comments on Problem Formulation for the Risk Evaluation of
NMP to Be Conducted under TSCA; Docket ID Number EPA-HQ-
OPPT-2016-0743

Dear Sir or Madam:

The N-Methylpyrrolidone (NMP) Producers Group, Inc.¹ submits these comments, which include the appended July 30, 2018, letter from Summit Toxicology, in response to the U.S. Environmental Protection Agency's (EPA) problem formulation for the risk evaluation of NMP to be conducted under the Toxic Substances Control Act (TSCA) (83 Fed. Reg. 26998 (June 11, 2018)). We appreciate the opportunity to comment.

**EPA Problem Formulation Does Not Reference
2016 EPA Supplemental Risk Assessment**

The NMP Producers Group is surprised and disappointed that the EPA problem formulation does not reference its "Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal [RIN 2070-AK07]" (Nov. 7, 2016). The November 2016 supplemental report is not included in the problem formulation list of references, nor is it included in the list of "on topic" references in the EPA bibliography. If EPA does not intend to utilize that report, it should indicate why and formally rescind the report and its findings.

¹ The NMP Producers Group includes domestic manufacturers of NMP and was formed to address efficiently and comprehensively regulatory and stewardship issues pertinent to NMP.

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EPA Must Address Point of Departure (POD) Derivation Errors in the 2015 Risk Assessment

EPA must correct the POD errors from the 2015 risk assessment. The NMP Producers Group is concerned that its extensive comments to EPA on its initial and supplemental risk assessments for paint removers containing NMP have been ignored. As detailed in those comments (appended), EPA's inappropriate use of an unusually and indefensibly low benchmark response rate (BMR) in the 2015 risk assessment results in an excessively low POD value. The NMP Producers Group's concern that EPA will repeat this same error is supported by multiple references in the problem formulation document to the 2015 risk assessment POD values.

As already noted in past comments and again emphasized in the appended Summit Toxicology letter, EPA should rely on a BMR of 1 standard deviation. This approach is standard practice with modeling continuous data sets and results in a POD value that is 2.6-fold higher than the EPA 2015 value.

EPA Must Address Other Errors in the 2015 Risk Assessment

The NMP Producers Group is particularly concerned with EPA's previous omission of a saturated air concentration value in its indoor air modeling, which resulted in modeled air concentrations for certain exposure scenarios exceeding the known saturated air concentration for NMP. EPA must be more diligent in ensuring that any modeling used is appropriately limited to reflect the physical and chemical parameters of the subject chemical. NMP has a known saturated air concentration value; EPA cannot assess risk for values that exceed that amount. This is particularly important because the input of the modeled air concentrations in the physiologically based pharmacokinetics (PBPK) model impact predicted blood measures, which impact anticipated hazard and associated risk. As noted in the Summit Toxicology letter, correction of this error results in predictions for peak NMP in blood four to 71 percent lower than reported in the EPA 2015 risk assessment report.

EPA Literature Review Missing Key Glove Permeation Report

The NMP Producers Group conducted a review of the references identified by EPA as "on topic" for the NMP risk assessment. The report "Assessment of the Efficacy of Different Glove Materials for Reducing Potential Hazards Associated with NMP-Containing Paint Strippers" was not included. The NMP Producers Group is particularly concerned with EPA's omission of this report, as it was conducted specifically for the NMP evaluation under the TSCA Work Plan program and was submitted directly to EPA by the NMP Producers Group.

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We believe that the analyses provided in that report are specifically applicable to EPA's assessment of NMP and provide critical information for the ongoing risk assessment.

EPA Should Incorporate the Use Information Previously Provided by Stakeholders

The NMP Producers Group is disappointed that the EPA problem formulation does not reference or reflect the use information provided by the Group in March 2017 in response to EPA's request for information on the use of NMP. That submission included workplace processing and exposure information for numerous industry sectors that were collected solely to assist EPA in the risk evaluation.

Likewise, the EPA problem formulation does not reference the detailed submission by the National Electrical Manufacturers Association (NEMA). EPA specifically requested that industry stakeholders engage in the risk assessment process and provide information to assist EPA in establishing the scope of the risk assessment. If EPA has made a decision that the information collected and submitted by the NMP Producers Group and other stakeholder associations is not relevant for its risk assessment activities, it should clearly indicate this and provide a detailed explanation as to why.

Correction of Physical and Chemical Characteristic Values

It is disappointing that EPA continues to ignore the information included in the Organization of Economic Cooperation and Development's (OECD) Screening Information Data Set (SIDS) dossier for NMP, particularly since EPA was the lead authority on that document. The NMP Producers Group highlights below where the EPA values in the problem formulation document differ from those in the OECD SIDS document.

	EPA Form	SIDS (OECD)
Physical Form	colorless to yellow liquid	colorless
Melting Point	-25 °C	-23.5 °C
Boiling Point	202oC	204.1 - 204.4 °C @ 1013 hPa
Vapor Pressure	0.345mmHg @25 °C	0.32hPa @20 °C

We recommend that EPA rely on the values from the OECD SIDS document, as those have been accepted globally under the OECD program.

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EPA Should Not Rely on Modeled Data if Actual Data Exist

The NMP Producers Group supports EPA's intention to use *in silico* tools to predict potential exposure, but only for endpoints in which actual data do not exist. If actual data exist, EPA should use those data and should not rely on modeled information.

EPA Should Not Presume Dust Potential for NMP

In several instances in the problem formulation, EPA references dust as a potential form for NMP. The NMP Producers Group notes that there are no powder forms of NMP available, so it is inappropriate for EPA to assume that a dust form exists.

EPA Should Not Presume NMP Will Be Heated

In several instances, the EPA problem formulation document references uses of NMP in which the NMP could be heated. The NMP Producers Group does not support any type of use activity in which NMP is heated. While we understand that EPA may have information that the heating of NMP has occurred by one particular niche use sector, this type of use would be counter to the specific instructions included on the NMP safety data sheet (SDS), which clearly indicate that heat sources should be avoided. The misuse of NMP in this fashion should not be presumed to be a typical or expected action, and should not be the basis for EPA risk management decisions.

Dermal Irritancy Potential of NMP Will Limit Consumer Exposures

In its problem formulation document, EPA fails to consider that the dermal irritancy potential of NMP will limit NMP dermal contact. If a consumer fails to wear appropriate gloves as specified, the consumer will experience skin irritation that will cause the consumer to stop using the product in an unprotected manner. It is unreasonable to assume that a consumer will continue to use an irritating product for more than a few minutes. This time limitation factor should be included in future EPA assessment calculations.

Dimethylformamide Is Not an Appropriate Surrogate to Assess NMP Exposure Potential

EPA's proposal to use dimethylformamide (DMF) as a surrogate for NMP exposure is inappropriate. DMF is six times more volatile than NMP. Its physical and chemical

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properties are not comparable to NMP. While DMF may have similar uses (*e.g.*, use as a solvent), it is not an acceptable surrogate chemical.

EPA Should Not Include Consumer Oral Exposure in Risk Assessment

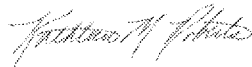
The NMP Producers Group questions the relevance of the oral exposure route for consumers and questions the utility of including it in the risk assessment. If EPA proceeds with its inclusion, EPA needs to provide additional details as to how it intends to assess risk of oral exposures for consumers. For example, will this be conducted on an internal or external dose basis? Will EPA remain focused on pregnant women as the sensitive subpopulation as it has done in its past risk assessments on NMP?

EPA Should Not Assess Separately Upper Airway Deposit of NMP in Risk Assessment

The NMP Producers Group does not believe that the potential of upper airway deposits of NMP need to be assessed separately. Based upon the rapid absorption of NMP at the point of contact, the incidental ingestion of inhaled NMP in the upper respiratory tract should be assumed to be negligible.

Thank you for the opportunity to submit these comments. If there are any questions regarding this letter, please do not hesitate to contact me at 202-833-6581 or kroberts@bc-cm.com.

Respectfully submitted,



Kathleen M. Roberts
NMP Producers Group Manager

Attachments

cc: Ms. Ana Corado (via e-mail) (w/attachments)

ATTACHMENT 1



PO Box 3209
Bozeman, MT 59715
406-224-0193
ckirman@summittoxicology.com

July 30, 2018

Kathleen M. Roberts
B&C Consortia Management LLC
2200 Pennsylvania Avenue, N.W. Suite 100W
Washington, D.C. 20037
T: 443-964-4653

Re: Summit Toxicology Comments on USEPA's Problem Formulation Report for NMP

Dear Ms. Roberts:

Summit Toxicology has reviewed USEPA's report entitled, "*Problem Formulation of the Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-) CASRN: 872-50-4*" (USEPA, 2018), and has developed a set of comments on select key issues. Please feel free to incorporate these comments into your submission to USEPA. Should you have any questions, please contact me via phone or email using the information below.

Best Regards,

Christopher Kirman
Principal
Summit Toxicology, LLP
Bozeman, MT 59715
Phone: 406-224-0193
Email: ckirman@summittoxicology.com

Comment 1: Please Ensure Concerns with USEPA's Previous TSCA Assessment and Supplemental Assessment (USEPA, 2015, 2016) are Addressed in the Future Risk Assessment.

We have previously submitted comments to USEPA regarding their report “*Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal [RIN 2070-AK07]*” (USEPA, 2016), which relied upon the toxicity assessment conducted previously (USEPA, 2015). To the extent USEPA’s future risk assessment relies upon the dose-response and exposure assessment decisions in these reports, we would like to remind USEPA of potential errors and inappropriate assumptions that we commented on previously (Summit Toxicology, 2017)¹, to prevent them from reoccurring in the future assessment for NMP:

- A. USEPA’s Benchmark Response of 1% Selected for Characterizing Fetal Resorptions is Inappropriate (details on page 2 of Summit Toxicology, 2017): *We recommend that USEPA rely upon a default benchmark response rate of 1 standard deviation (BMDL1SD=548 mg/L, as reported in USEPA’s Table_Apx H-8) for consistency with standard practice with modeling continuous data sets, which results in a POD value that is 2.6-fold higher than EPA’s selected value (i.e., 548 mg/L / 248 mg/L).*
- B. The Exposure Durations Used in USEPA’s Acute Toxicity Assessment and Acute Exposure Assessments for NMP Are Discordant, Resulting in an Overestimation of Potential Hazard (details on page 5 of Summit Toxicology, 2017): *We recommend that any exposure duration concordance issues be resolved. For example, USEPA’s 15-day POD value of 216 mg/L should be adjusted to be 2.3-fold higher (492 mg/L) to assess acute, 1-day exposure scenarios for consumers and workers based upon an analysis of the data of Schmidt et al. (1976) for NMP and fetal absorptions.*
- C. USEPA Appears to Have Omitted Including a Value For Csat In Its Modeling To Predict Indoor Air Concentrations, Resulting In An Overestimate Of Exposures To NMP (details on page 6 of Summit Toxicology, 2016): *Inspection of the following support file for the 2016 supplemental report (76_1_Appendix_B_SUPPL_Analysis_Consumer_NMP_paint_removal.xls) reveals modeled air concentrations as high as 7,771 mg/m³ for NMP, which is well above the reported range for Csat (640-1,013 mg/m³). We recommend that USEPA incorporate Csat in its air modeling for the supplemental report, as was performed in its 2015 assessment. In so doing PBPK model predictions for peak NMP in blood that are expected to be 4%-71% lower than presented in USEPA’s supplemental report (USEPA, 2016).*
- D. Many of the Exposure Assumptions Used by USEPA are Expected to Overestimate Actual Exposures to NMP (details on page 8 of Summit Toxicology, 2017): *We recommend USEPA modify their assessment as follows: (1) For all exposure scenarios except for application to floors, exposure scenarios should be account for the most likely exposure scenarios involving moving items to be stripped outdoors/to garage prior to NMP application; (2) For the small, unventilated room scenarios (e.g., bathtub stripping), two additional options should be included to account for higher air change rates associated “Window Open” and “Exhaust Fan On”; and finally (3) For consumer and worker*

¹ RIN 2070-AKOT, Prepared by Christopher R. Kirman and Torka S. Poet, from Summit Toxicology, April 11, 2017.

exposure scenarios that are inconsistent with product labeling instructions, these should be labeled and presented separately as “Product Misuse Scenarios” so that risk management options for these scenarios can be addressed independently from “Product Use Scenarios”.

- E. Parameter Values Used in USEPA’s PBPK Model Are Overly Conservative:
Parameterization of the human PBPK model differed between USEPA (2015) and Poet et al., 2016, particularly with the selective treatment of the Bader et al. (2008) by USEPA. The impact of the model parameterization is discussed in Poet et al. (2016). We recommend that USEPA use human parameter values that are appropriate for the concentration range of interest (i.e., near the POD values), rather than those that were specifically optimized for low concentrations of NMP. As compared in Poet et al. (2016), the corresponding POD values are approximately 20-30% higher than calculated in USEPA (2015).

Comment 2: Characterization of Important Exposure Pathways for NMP Needs to be Assessed Equitably for the Exposure and Toxicity Components of the Risk Assessment to Avoid Potential Mischaracterization of Hazard

On page 60 of the problem formulation document, USEPA (2018) states, “Dose-response analyses performed to support the TSCA Work Plan Chemical Risk Assessment on NMP use in Paint Stripping U.S. EPA (2015) may be used if the data meet data quality criteria and if additional information on the identified hazard endpoints or additional hazard endpoints would not alter this analysis.” Although there are positive aspects to the dose-response assessment of USEPA (2015), including the use of physiologically based pharmacokinetic (PBPK) modeling and benchmark dose (BMD) modeling, there are some important limitations. For example, USEPA’s problem formulation indicates that the risk evaluation of NMP will consider up to 4 exposure pathways in the assessment of potential exposures to workers and consumers (incidental ingestion, inhalation of vapors, dermal absorption of vapors, dermal absorption of liquids). Inclusion of these pathways is appropriate in the human exposure assessment for NMP. However, this also introduces an inequitable treatment of NMP dose in the exposure and toxicity components of the margin of exposure (MOE) calculations for NMP, as is illustrated in **Figure 1**.

Figure 1. Illustration of Potential Mischaracterization of NMP Hazard in MOE Calculations

Margin of Exposure (MOE) =	NMP Dose from Toxicity Assessment (rat toxicity-based POD)			
	Ingestion of NMP adsorbed to fur during grooming was not assessed by EPA	Inhalation of NMP vapor was assessed by EPA	Dermal absorption of NMP vapor was not assessed by EPA	Dermal of NMP liquid not applicable under conditions of inhalation toxicity studies
	NMP Dose From Exposure Assessment (human exposure scenarios)			
	Incidental ingestion will be assessed by EPA	Inhalation of vapor will be assessed by EPA	Dermal absorption of vapor will be assessed by EPA	Dermal absorption of liquid will be assessed by EPA

Specifically, USEPA's toxicity assessment conducted for NMP considers only the inhalation of NMP vapor for under the conditions of the NMP inhalation toxicity studies (whole-body exposures) in deriving the point of departure of 48 mg/kg-day (referenced on pages 47, 48) and its equivalent inhalation concentration (263 mg/m³, referenced on page 49) for developmental effects. In contrast, a fuller characterization of exposure pathways is anticipated for the human exposure assessment. By underestimating the numerator in the MOE calculation, the margin of exposure value calculated may be lower than its true value, and the magnitude of the underestimation is likely significant. As discussed in Poet et al. (2016) the exposure pathways issue is due in part to the PBPK model's reliance upon a nose-only exposure study for model parameters. Specifically, air exposures to rats were parameterized in the PBPK model from a nose-only exposure study (Ghantous, 1995) and subsequently used in this assessment to predict internal doses resulting from whole-body exposures to rats (Saillenfait et al., 2003; Solomon et al., 1995). Therefore, in rats, model predictions for whole-body exposures for developmental toxicity studies do not include any contributions from dermal uptake of vapors or oral uptake via grooming (pathways depicted in red in **Figure 1**). If these pathways are sufficiently important to assess in humans, then these pathways are likely even more important to consider in the rat toxicity studies for the following reasons:

- (1) With respect to the dermal vapor pathway, there is clear evidence that this pathway is important in humans since the combined contributions from inhalation and dermal absorption of vapor (when wearing trousers and short-sleeved shirts) to the internal dose were 1.5- to 1.7-fold higher than that from inhalation alone (Bader et al., 2008). McDougal et al. (1990) reported that the dermal permeability coefficients for organic chemical vapors were 2- to 4-times greater in rats compared to humans, suggesting the fold impact of the dermal vapor pathway in rats would be even higher.

- (2) With respect to sorption of vapors on to fur and ingestion while grooming, this pathway has been shown to be potentially significant for other chemicals, including 2-butoxyethanol (Poet et al., 2003), 1,1,2,2-tetrachloroethane (Gargas and Andersen, 1989), and ethylene glycol (Tyl et al. 1995). Because of grooming behavior in rats, the oral dose received from fur is expected to be considerably higher than the incidental ingestion of vapors in humans.

We estimated that if these two pathways combine to increase the total NMP dose delivered to rats via whole-body exposures by a factor of 3.3-fold compared to vapor inhalation alone, the apparent discrepancy in NMP potency for oral vs. inhalation exposures for developmental toxicity would be resolved (i.e., concordance across route of exposure) (Poet et al., 2016). We recommend that USEPA include quantification of these two pathways when deriving POD values from rat studies for inhalation exposures to NMP, so that any errors in MOE calculation are avoided. Such an approach would be consistent with USEPA's statement on page 40 that correctly notes that *"More severe effects have been noted following whole-body inhalation exposure (which includes dermal and oral uptake)"*

Comment 3: Additional Details on CEM Model Implementation Should Be Included

USEPA's problem formulation document indicates that the Consumer Exposure Model (CEM), which is a screening level model, will be used instead of the Multi-Chamber Concentration and Exposure Model (MCCEM), a higher tier model that was used in USEPA's 2015/2016 assessments. With respect to implementing the CEM model, we recommend consideration of the following points:

- CEM does permit setting a saturation limit for modeled emissions. As stated above, please ensure that modeled air concentrations do not exceed saturable air concentrations (C_{sat}) for NMP. C_{sat} for NMP is dependent upon air humidity and can range from 640 to 1,013 ppm. Unfortunately, several examples of modeled air concentrations exceeding C_{sat} persisted in USEPA's supplemental assessment for NMP (USEPA, 2016).
- While the benefit of including additional exposure pathways by using CEM is recognized, as a screening level model, there is concern that the model may predict unrealistic exposure concentrations. To the extent possible, CEM should be validated against measured air concentrations. The data from the USEPA study of consumer exposures to paint stripper solvents (USEPA, 1994), would serve as excellent check on the degree to which the CEM model predictions agree or disagree with measured values under worst-case conditions.
- In USEPA (2015, 2016), the results of the MCCEM model were used as inputs into the PBPK model developed for NMP, to account for species differences in NMP clearance (i.e., human>rats) and to account for total NMP dose across multiple routes of exposure. In the NMP formulation report, the PBPK model is mentioned only briefly on page 57. It is not clear from the formulation document if USEPA anticipates integrating the output from the CEM model with the PBPK model in a similar manner. Please provide detail on these models will be integrated.

Comment 4: The need for and selection of an exposure data surrogate requires consideration

On page 56 of the problem formulation document, USEPA identifies dimethylformamide as a potential surrogate for NMP exposure. This is problematic for two reasons: (1) It is not clear that an exposure surrogate is needed for NMP, since adequate exposure data appear to be readily available; and (2) Based upon a comparison of the chemical properties (**Table 1**), dimethylformamide does not appear to sufficiently similar to NMP.

Table 1. Comparison of Chemical Properties of NMP and Dimethylformamide*

Property	NMP	Dimethylformamide	Fold Difference
Vapor Pressure (mm Hg, 25 deg C)	0.345	3.87	10x
Octanol-Air Partition Coefficient	229,000	32,000	7x
Henry's Law Constant (atm-m ³ /mole)	3.16E-08	7.38E-08	2.3x

*Data from ChemSpider (www.chemspider.com; Episuite predicted values)

Based upon a comparison of these properties, dimethylformamide is expected to be considerably more volatile than NMP, and therefore its use as an exposure surrogate is not appropriate. We recommend that surrogate chemicals not be used to support the assessment for NMP.

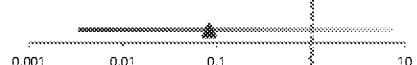
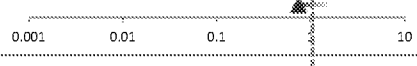
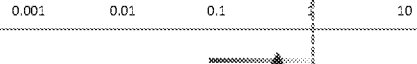
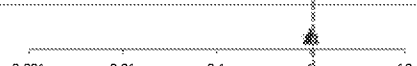
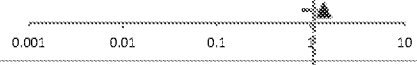
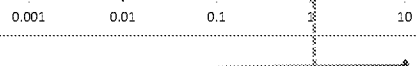
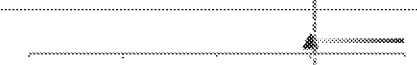
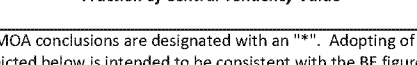

Comment 5: Data sources of PPE should include the report entitled, "INSERT", submitted to the TSCA docket for NMP

On page 57 of the problem formulation report, USEPA states, "EPA will review potentially relevant data sources on engineering controls and personal protective equipment as identified in Table_Apx B-7 and determine their applicability for incorporation into specific exposure scenarios during risk evaluation." Previously Summit Toxicology prepared report entitled, "Assessment of the Efficacy of Different Glove Materials for Reducing Potential Hazards Associated with NMP-Containing Paint Strippers," which was submitted to the docket for the NMP TSCA assessment (Summit Toxicology, 2015), but is missing from the references to be considered in Table Apx B-7. In this report, a refined risk assessment was conducted to evaluate the efficacy of different glove materials for reducing the potential hazards associated with using paint strippers containing NMP under the scenarios defined by USEPA's TSCA risk assessment. USEPA's PBPK model was slightly modified to accommodate the inclusion of published glove permeation rates for NMP. The results of this assessment indicate that NMP-containing paint strippers can be used safely when appropriate PPE are used and can be used to support risk-reduction methods (e.g., product labeling, MSDS instructions on use of appropriate glove materials) as alternatives to banning NMP use under TSCA. We recommend that the Summit Toxicology assessment on glove efficacy be included in Table Apx B-7 for consideration in the future risk assessment for NMP.

Comment 6: USEPA Should Consider Inclusion of Additional Tools to Facilitate Transparency and Communication of Uncertainty in the Risk Assessment

On page 61 of the problem formulation report, USEPA states “EPA will further carry out the obligations under TSCA section 26; for example, by identifying and assessing uncertainty and variability in each step of the risk evaluation,” and goes on to state that USEPA will identify “the expected risk or central estimate of risk for the potentially exposed or susceptible subpopulations affected.” We agree that these are worthy goals for the future NMP risk assessment, and would like to make USEPA aware of a recent publication, “Approaches for describing and communicating overall uncertainty in toxicity characterizations: U.S. Environmental Protection Agency’s Integrated Risk Information System (IRIS) as a case study” that includes the description of a tool that can be used to accomplish these goals (see Table 9 of Beck et al., 2016). The uncertainty tool is depicted in **Figure 2**, using the IRIS assessment for acrylamide as an example, and shows the underlying decisions in the dose-response assessment (each row of the table), while depicting the range of possible options (horizontal blue bar), central tendency values (vertical dashed line), and the value selected by USEPA in the assessment (red triangles). This uncertainty tool provides an “at-a-glance” summary of the decisions made in the risk assessment, hi-lighting those that are critical (i.e., those with the widest range of options), as well as those that are over- or under-protective (i.e., large deviations from central tendency). We recommend that USEPA consider including this tool as part of the executive summary of the future TSCA risk assessments for NMP and other chemicals.

Figure 2. Example Characterization of Uncertainty in Dose-Response Assessment Decisions (acrylamide as an example; from Beck et al., 2016)

Decision Point	Range of Options**	Central Tendency	Selected	Confidence in Selection (Science- or Policy-based)
Mode of Action Assessment*	Neurotoxicity mediated by acrylamide Neurotoxicity mediated by glycidamide	Mediated by acrylamide	Mediated by acrylamide	?
Data Set/Endpoint Selection*		Mean NOAEL across studies in Table 5-1	NOAEL for peripheral nerve effects (Johnson et al)	Medium/High confidence in key study (Policy decision to be protective)
Dose-Response Model Selection		Mean POD of acceptable models	Log-logistic model	?
Confidence Limit Selection		POD = BMD	POD = BMDL	?
Benchmark Response Rate Selection		BMR = 10%	BMR = 5%	?
Rat Internal Dose Calculation*		Mean AAVal Slope = 7.5×10^{-6} L/g-hr	AAVal Slope of 7.5×10^{-6} L/g-hr	Science decision to be predictive
Human Equivalent Dose Calculation*		Mean AAVal In Vitro Rate = 5.4×10^{-6} L/g-hr	AAVal In Vitro Rate = 7.5×10^{-6} L/g-hr	Science decision to be predictive
Interspecies Variation (UFa)		1 (assume humans and rats are equally sensitive)	3 (assume that humans are 3x more sensitive than rats)	Policy decision to be protective
Intraspecies Variation (UFh)		1 (for average individual)	10 (assume some individuals are 10x more sensitive)	Policy decision to be protective
Duration Extrapolation (UFs); LOAEL-to-NOAEL Extrapolation (UFI); Database Uncertainty (UFd)		1 for each	1 for each (key study is chronic; BMD methods used; database is complete)	?
	Fraction of Central Tendency Value	dose = ~3 mg/kg-day	RfD = 0.002 mg/kg-day	Medium/High confidence in RfD

Decision points that are impacted by MOA conclusions are designated with an "". Adopting of a different MOA conclusion may yield alternative results for these decision points

**The shading gradient of the lines depicted below is intended to be consistent with the BE figure gradient. Values in the dark blue region result in lower RfDs than the light blue region.

References:

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ATTACHMENT 2



N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.

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May 19, 2017

Via Docket Submission

Document Control Office (7407M)
Office of Pollution Prevention and Toxics (OPPT)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460-0001

Re: Comments on Regulation of Certain Uses of N-Methylpyrrolidone
under TSCA; Docket ID Number EPA-HQ-OPPT-2016-0231

Dear Sir or Madam:

The N-Methylpyrrolidone (NMP) Producers Group, Inc.¹ submits these comments in response to the U.S. Environmental Protection Agency's (EPA) proposed rulemaking to regulate certain uses of NMP under Section 6 of the Toxic Substances Control Act (TSCA) (82 Fed. Reg. 7464 (Jan. 19, 2017)). This submission by the NMP Producers Group focuses on process issues and scientific concerns related to the risk assessments conducted by EPA, which are the basis for the TSCA Section 6 risk management proposed rulemaking. The NMP Producers Group will be providing a separate submission regarding the specific proposed restriction options outlined in the *Federal Register* notice.

Background

The initial EPA risk assessment on NMP conducted under the TSCA Work Plan Chemicals program was issued in March 2015.² The scope of the March 2015 assessment included occupational paint stripping applications (acute and chronic exposures, including workers that may be nearby) and consumer paint stripping applications (acute, including other

¹ The NMP Producers Group includes domestic manufacturers of NMP and was formed to address efficiently and comprehensively regulatory and stewardship issues pertinent to NMP.

² EPA, "TSCA Work Plan Chemical Risk Assessment, N-Methylpyrrolidone: Paint Stripper Use, CASRN: 872-50-4" (Mar. 2015), available at https://www.epa.gov/sites/production/files/2015-11/documents/nmp_ra_3_23_15_final.pdf.



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residents that may be nearby).³ The March 2015 assessment did not include chronic consumer exposures. In the March 2015 risk assessment report, EPA calculated Margins of Exposure (MOE) for various application scenarios of NMP paint strippers, and compared them to a benchmark MOE of 30 to determine if unacceptable risks were present. MOEs below 30 indicate the presence of risks. In the final assessment report, EPA identified one consumer use scenario with an MOE of 29.5, but also noted that this value was considered to be equivalent to the benchmark MOE of 30, indicating low risk. All other consumer use scenarios were above 30.⁴ Thus, the final risk assessment did not identify risk with *any* consumer use scenario evaluated.

In March 2016, and again in June 2016, EPA presented information on the NMP risk assessment to stakeholders.^{5,6} The information presented stated “[r]isks were identified for a number of worker and consumer exposure scenarios,” which contradicts the March 2015 final report. After numerous outreach efforts by the NMP Producers Group, EPA conceded in an August 2, 2016, letter that additional analyses had been conducted and that the supplemental work informed the risk management on the consumer risk scenarios.⁷ EPA also noted that the supplemental analysis would not be available for public review until the issuance of the proposed Section 6 risk management rule.

³ *Id.* at 23.

⁴ *Id.* at 88 and 89.

⁵ EPA Power Point Presentation for Small Entity Representatives (SER), “Rulemaking for Methylene Chloride and N-Methylpyrrolidone (NMP) under the Toxic Substances Control Act (TSCA)” (Mar. 17, 2016).

⁶ EPA Power Point Presentation for SERs, “Rulemaking for Methylene Chloride and N-Methylpyrrolidone (NMP) under the Toxic Substances Control Act (TSCA)” (June 15, 2016).

⁷ Letter from Dr. Jeffery T. Morris, EPA Deputy Director for Programs, Office of Pollution and Toxics, to Kathleen M. Roberts, Manager, NMP Producers Group (Aug. 2, 2016).



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EPA Cannot Rely on Supplemental Analysis for Section 6 Rulemaking

The NMP Producers Group believes EPA's approach to issue the supplemental risk assessment on NMP, concurrent with the proposed Section 6 rulemaking, violates Section 26(l)(4), which states:

With respect to a chemical substance listed in the 2014 update to the TSCA Work Plan for Chemical Assessments for which **the Administrator has published a completed risk assessment prior to June 22, 2016**, the Administrator may publish **proposed and final rules under section [6(a)] that are consistent with the scope of the completed risk assessment** for the chemical substance and consistent with other applicable requirements of section [6].⁸

This language is clear. EPA may only issue a Section 6(a) proposal that is consistent with the scope of the completed risk assessment. In the case of NMP, the completed risk assessment issued in March 2015 did not identify consumer exposures as a risk. EPA did not publish an updated risk assessment incorporating the findings of the supplemental risk assessment prior to June 22, 2016 (enactment of new TSCA). As such, any Section 6 action on NMP cannot include restrictions associated with consumer uses unless and until EPA reissues an updated assessment for review.

Questionable Timing of EPA Supplemental Risk Assessment and Announcement of Assessment Conclusions

The NMP Producers Group questions the timing of the supplemental risk assessment on NMP in conjunction with EPA public statements on risk findings. As noted, the initial risk assessment was issued in March 2015, and that assessment indicated no consumer risk associated with paint removers containing NMP. In March 2016, and again in June 2016, EPA made clear statements regarding findings of consumer risk associated with paint removers containing NMP. These presentations did not indicate that the information presented was preliminary or draft. Nor did the presentation reference a completed or ongoing supplemental risk assessment. In fact, the only reference in the presentations to a risk assessment was the March 2015 assessment.

⁸ TSCA § 26(l)(4), 15 U.S.C. § 2625(l)(4) (emphasis added).



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The supplemental risk assessment report, which identified scenarios of consumer risk, is dated November 2016.⁹ This is seven months *after* EPA's presentation in March 2016 in which EPA clearly and definitively stated findings of consumer risk. The NMP Producers Group questions how EPA staff was able to present findings on a supplemental risk assessment in March if that risk assessment was not completed until November. If the findings presented were based on the ongoing supplemental analysis, they should have been clearly identified as preliminary or draft. That was not the case.

At best, EPA's statements from March and June 2016 are misleading. At worst, it appears that EPA made the decision to pursue risk management on consumer uses, despite the findings of the March 2015 assessment report, and worked backwards to identify potential consumer risk scenarios that supported that decision. As further outlined below, the scenarios and calculated risk thresholds identified by EPA in the supplemental assessment are not scientifically appropriate and cannot be used as the basis for risk management actions. As such, EPA should not proceed with risk management actions, as they are based on flawed assumptions and calculations.

Risk Assessments Flawed -- Summit Toxicology Review

There are numerous and significant flaws in the supplemental risk assessment -- flaws that EPA would have become aware of had it issued the assessment for public and peer review, as the NMP Producers Group had asked. As issued, the supplemental assessment and its findings are not scientifically appropriate or relevant, and EPA cannot base a decision to proceed with risk management based on those findings.

The NMP Producers Group retained Summit Toxicology to conduct an analysis of the EPA supplemental risk assessment for NMP. In its preliminary analysis, Summit Toxicology identified multiple areas of concern, including EPA's choice for key endpoints (fetal resorptions versus skeletal malformation), dose measure (peak NMP in blood versus area under the curve (AUC)), and exclusion of efficacy consideration for glove material. Due to time and resource limitations, however, the NMP Producers Group and Summit Toxicology could not conduct a comprehensive evaluation of each area of concern. Instead, the NMP Producers Group directed Summit Toxicology to focus its evaluation on three key issues: (1) benchmark dose response;

⁹ EPA, "Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal [RIN 2070-AK07]" (Nov. 7, 2016).



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(2) exposure estimations -- window of susceptibility; and (3) reliance on air concentrations exceeding saturation.

The detailed Summit Toxicology report will be submitted separately by Summit Toxicology and is also appended to these comments. The key findings are:

1. EPA's selection of an unusually low benchmark response (BMR) rate, along with an inappropriate assumption of equivalence for 1-day and 15-day exposures to NMP, results in a point of departure value that is lower than can be supported by NMP-specific data, and should be approximately 5.9-fold higher ($C_{max} = 1,260$ mg/L for NMP in blood).
2. EPA's decision to omit the saturated air concentration value of NMP that it is air modeling resulted in an overestimation of predicted exposures for consumer use scenarios, and should be approximately 4 percent to 71 percent lower.

Importantly, correcting for these scientific errors results in MOE values for all consumer scenarios above a value of 30, indicating that the potential risks associated with these scenarios are negligible, meaning no risk management actions are necessary.

EPA Peer Reviewer Highlights Additional Analysis Flaws

In a separate submission, Dr. Tom Armstrong, an expert who participated in the peer review of the initial methylene chloride and NMP peer review meetings, highlights serious errors in the initial NMP assessment that were identified to EPA, but were ignored.¹⁰ Armstrong notes that two main flaws occurred in the initial exposure assessment for NMP that impact the risk assessment findings. The first is that EPA used an inappropriate value (first order exponential) of the evaporation of NMP from a paint stripper application. Based on Armstrong's review, it appears that EPA used the methylene chloride value in its NMP assessment. Armstrong highlighted this potential error to EPA during the peer review process, and was informed by EPA that it does not matter. As Armstrong notes, however, it is not possible for NMP, which has a vapor pressure of 0.19 Torr, to have the same evaporation value as methylene

¹⁰ Armstrong, T., "Comparison of EPA Results to Alternative Inhalation Exposure Assessment and Risk Assessment Calculations for Example NMP Paint Stripping Use Scenarios" (Apr. 11, 2017).



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chloride, which has a vapor pressure of 400 Torr. The difference in vapor pressures between NMP and methylene chloride is a factor of over 4,000, yet EPA used the same evaporation value (E1 of 10) for both.

The second flaw highlighted by Armstrong is that EPA inappropriately used the saturated vapor pressure for pure NMP, rather than the partial pressure of NMP in a mixture. Armstrong re-ran the EPA Multi-chamber Concentration and Exposure Model (MCCEM) using the more correct NMP partial pressure value for several of the scenarios included in EPA's assessment. The results are summarized below:

- Brush-on Application on Coffee Table -- Using the vapor pressure for pure NMP, EPA incorrectly calculated a 90-minute Time Weighted Average (TWA) of 9.2 mg/m³. Using the partial vapor pressure and appropriate E1 value, Armstrong determined that the calculated 90-minute TWA would be 5.6 mg/m³ -- nearly half of EPA's calculated value.
- Spray-on Application on Coffee Table -- If the vapor pressure for pure NMP is modeled per EPA's scenario, the calculated 85-minute TWA is 24 mg/m³. Using the partial vapor pressure value and appropriate E1 value, Armstrong determined the calculated 85-minute TWA would be 14.7 mg/m³.
- Bathtub Refinishing -- EPA's calculated TWA for 2.8 hours is 688 mg/m³. Using the appropriate vapor pressure and E1 value, and corrected for relative humidity conditions, Armstrong calculated the TWA for 2.8 hours to be 81 mg/m³, almost eight times less than EPA's calculated value.

Further details on Armstrong's approaches are included in his submission. Given the potential impacts of the errors noted by Summit Toxicology and Dr. Armstrong, it seems evident that EPA must conduct an updated assessment, using appropriate scientific approaches and methodologies. That updated assessment should be vetted through peer and public review processes before EPA proceeds with any Section 6 risk management actions.

Initial EPA Risk Assessment Process for NMP Fraught with Problems

As outlined in the NMP Producers Group's April 26, 2016, letter in response to the May 11, 2016, orientation meeting of the Chemical Safety Advisory Committee (CSAC), the EPA NMP assessment under the TSCA Work Plan Chemicals program was highly problematic. Although EPA solicited stakeholder engagement, it was difficult to achieve, given EPA's lack of



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transparency on what it already conducted and what specific information it was seeking. In addition, the peer review process was rushed, and specific scientific input provided to EPA by the NMP Producers Group was not shared with the committee, nor posted in the public docket.

EPA issued a draft assessment in December 2012. The NMP Producers Group submitted extensive comments in April 2013. Included in the NMP Producers Group comments was a recommendation that EPA utilize a physiologically-based pharmacokinetic (PBPK) model for NMP, which EPA eventually did. While the NMP Producers Group is supportive of that decision, the result was essentially the generation of a completely new risk assessment document, which was issued two weeks prior to the second peer review meeting. Despite requests from the NMP Producers Group to reissue the draft assessment, EPA did not, which meant there was no public comment period afforded the new assessment and limited peer review.

Key recommendations on the updated draft assessment were submitted to EPA, but it is unclear whether they were considered, as there was neither an open docket nor a formal comment period. Below, we reiterate the concerns on the November 8, 2013, peer review committee discussion on the draft assessment approach from our November 22, 2013, submission to EPA (appended).

- The NMP Producers Group maintains that the plasma and urine data of Bader *et al.* (2007) and individual data provided in the unpublished report of Bader and van Thriel (2006) are consistent with linear toxicokinetics for NMP under the conditions of the study. There is, therefore, no reason to question or to make changes to the existing PBPK model for NMP.
- EPA should not adopt any recommendation from the peer review committee that does not comport with current EPA guidance and policy, including lowering the BMR for fetal body weights to 1 percent.
- EPA should not issue the NMP risk assessment using exposure values associated with scenarios of misuse.
- EPA should rely on empirical data over hypothetical modeling predictions to decrease uncertainties and increase the relevance of conclusions to real world exposures.

Given the problems associated with the supplemental risk assessment approach, and the issues encountered with the initial risk assessment, the NMP Producers Group sees no other alternative but for EPA to withdraw the proposed Section 6 rulemaking and re-issue the



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risk assessment for public and peer review. We also urge EPA to incorporate the re-issuance of the risk assessment as part of the ongoing NMP risk assessment on other conditions of use.

Thank you for the opportunity to submit these comments. If there are any questions regarding this letter, please do not hesitate to contact me at 443-964-4653 or [kroberts@bc-cm.com](mailto: kroberts@bc-cm.com).

Respectfully submitted,

A handwritten signature in black ink, which appears to read "Kathleen M. Roberts", is positioned below the "Respectfully submitted," text.

Kathleen M. Roberts
NMP Producers Group Manager

Attachments

*Comments on USEPA's "Supplemental
Consumer Exposure and Risk Estimation
Technical Report for NMP in Paint and
Coating Removal [RIN 2070-AK07]"*

Prepared by
Christopher R. Kirman and Torka S. Poet



April 11, 2017

Introduction

Summit Toxicology, LLP has been retained by the N-Methylpyrrolidone (NMP) Producers Group to review and submit comments on USEPA's supplemental report entitled "*Supplemental Consumer Exposure and Risk Estimation Technical Report for NMP in Paint and Coating Removal [RIN 2070-AK07]*" (USEPA, 2016). In this report, USEPA has extended to include 18 additional residential/consumer exposure scenarios, that are based on more high-end exposure assumptions than were included in the 2015 TSCA risk assessment. As we have stated in previous comments, USEPA should be commended for incorporating many best available science practices into its dose-response assessment for NMP, including: (1) the use of PBPK modeling to support conducting the risk assessment in terms of an internal dose measure and account for important species differences in NMP clearance; and (2) using the PBPK model to combine dose-response data sets across routes of exposure (oral and inhalation) to provide a more robust characterization of the dose-response relationships for NMP. Summit Toxicology strongly advocates for both of these practices. By the same token, on the exposure assessment side, it is recognized that USEPA's assessment represents a great deal of work, and USEPA's inclusion of the impact of glove use and open windows on their predicted exposure estimates for NMP is greatly appreciated. However, we also believe there remains room for improvement in USEPA's supplemental report, for which we offer comments on four specific issues, as described below.

Comment #1: USEPA's Benchmark Response Selected for Characterizing Fetal Resorptions is Inappropriate

In deriving an acute toxicity value for NMP, USEPA has applied PBPK modeling and benchmark dose methods to the combined data of Saillenfait et al. (2002, 2003) to determine the dose corresponding to a 1% increase in fetal resorptions (USEPA, 2015). In our experience with benchmark dose analyses, care should be taken to avoid selecting point of departure values in dose regions where the slope of the predicted dose-response curve approach extremes, whether the slope be approaching infinity (i.e., near vertical line) or zero (i.e., near horizontal line). In such cases, model predictions for the point of departure can become unstable and/or highly uncertain. In USEPA's characterization of fetal resorptions observed in rats exposed to NMP, they opted to rely upon a benchmark response rate of 1% relative deviation ($RD=1E-02$), which differs considerably from the standard practice of relying upon and benchmark response rate of 1 standard deviation used for continuous data sets. Unfortunately, use of such an unusually low benchmark response rate by USEPA puts the point of departure within the dose range where the Hill model predicts the slope of the dose-response curve to be essentially zero (i.e., below C_{max} values of approximately 500 mg/L) (**Figure 1**). The absence of fetal resorptions at low doses is supported by the results of several other studies that were not used to support the BMD analysis (Becci et al., 1982; Haas et al., 1995; Solomon et al., 1995).

Hill Model, with BMR of 0.01 Rel. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL

Dose	Mean Response	Lower CI	Upper CI
0	4	2	6
25	10	4	20
50	6	3	11
125	8	0	18
250	5	2	8
500	10	6	14
800	90	85	95

Mean Response

Dose

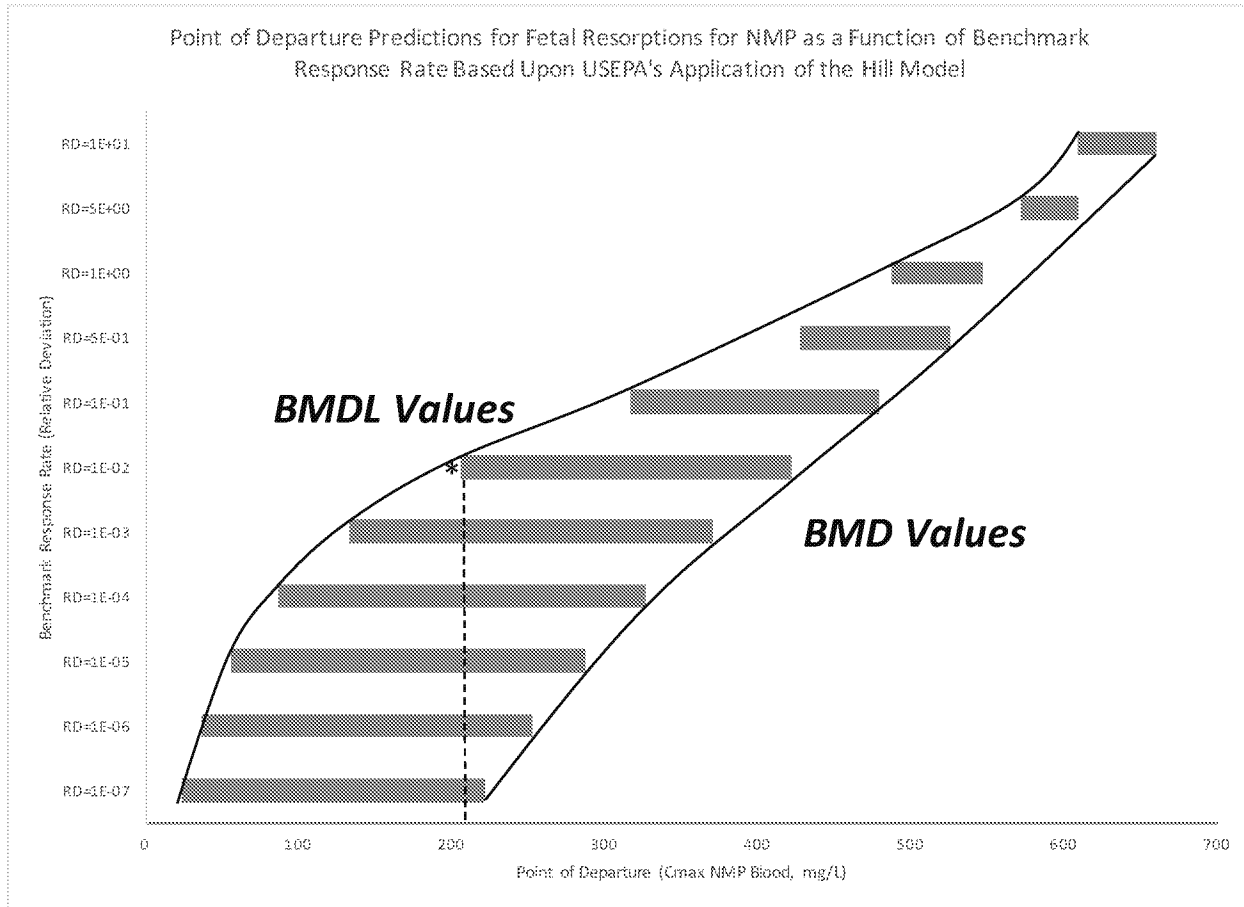
BMDL

BMD

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Figure 2. Impact of Benchmark Response Selection on Benchmark Dose Confidence Limits



In this figure, the range defined by the best fit (BMD, the right end of each bar) and the 95% lower confidence limit (BMDL, the left end of each bar) becomes increasingly wider (i.e., more uncertain) for lower benchmark response rates. Because the Hill model predicts that the slope of the dose-response relationship for resorptions below 500 mg/L is very near zero, it cannot be used to determine a response rate of 1% (depicted by the vertical dashed line) with reasonable confidence. To illustrate, the $BMDL_{RD=1E-02}$ value of 214 mg/L selected by USEPA is also approximately equivalent to the value for $BMD_{RD=1E-07}$ (i.e., a response rate uncertainty covering 5 orders of magnitude, which would be even wider if upper confidence limits in the BMDs were also considered). *For this reason, we recommend that USEPA rely upon a benchmark response rate of 1 standard deviation ($BMDL_{1SD}=548$ mg/L, as reported in USEPA's Table_Apx H-8) for consistency with standard practice with modeling continuous data sets, which results in a POD value that is 2.6-fold higher than EPA selected value of 214 mg/L.*

Comment #2: The Exposure Durations Used in USEPA's Acute Toxicity Assessment and Acute Exposure Assessments for NMP Are Discordant, Resulting in an Overestimation of Potential Hazard

USEPA's toxicity value for acute exposures is based upon studies that included a 15-day exposure period during gestation (GD6-20; Saillenfait et al., 2002, 2003). In contrast, USEPA's exposure assessment included a 1-day exposure assumption for residential/consumer scenarios. USEPA's default assumption that developmental effects could arise as a result of a single exposure (i.e., equivalence of 15-day and 1-day exposures) is a conservative one. The relationship between acute (single) exposures and repeated exposures in producing developmental effects has been examined for chemicals in general (van Raij et al., 2003). The study authors reported that for the 22 chemicals assessed for fetal resorptions, which serves as the key endpoint of concern for USEPA acute toxicity value, the acute doses producing effects were on average 2.1-fold higher than those associated with repeated doses. The results of this study would suggest that USEPA's 15-day POD value of 214 mg/L should be adjusted 2.1-fold higher (449 mg/L) for a single day exposure.

Fortunately, there are also NMP-specific data for which this issue can be addressed:

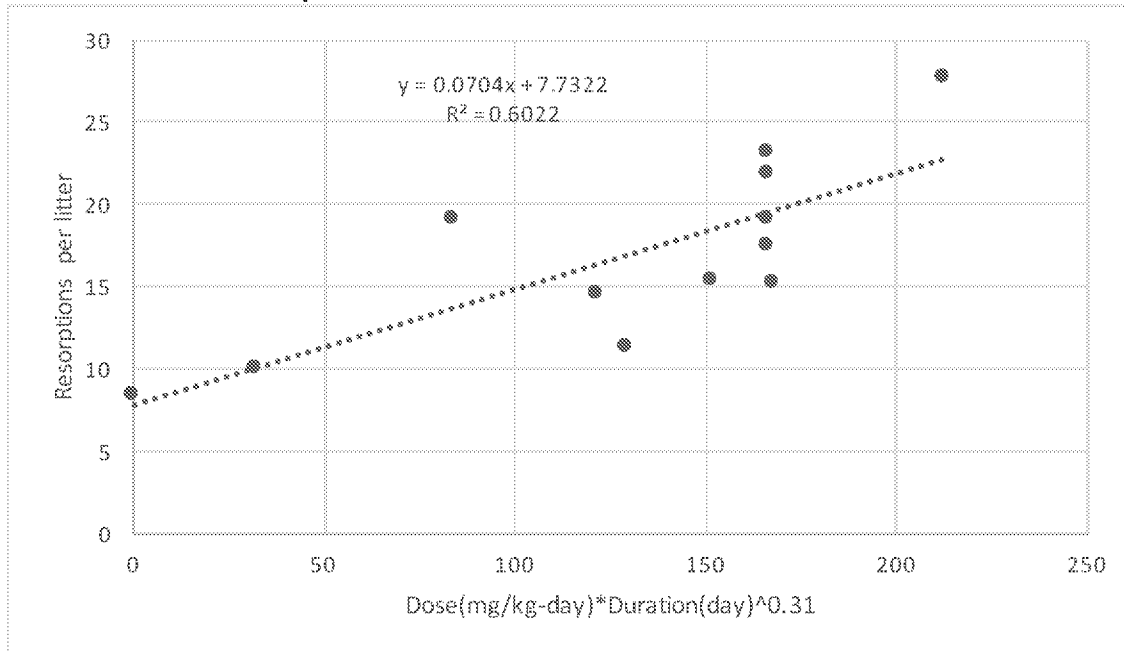
Schmidt VR. 1976. Experimental investigations about the embryotoxic and teratogenic effect of N-methyl-pyrrolidone (NMP). Biol. Rundsch. 14:38-41.

Schmidt et al. (1976) conducted study in mice that assessed the effect of multiple exposure periods for mice exposed to NMP via ip injection. This is an easy paper to miss (or dismiss) for acute toxicity value derivation since it is more than 40 years old, published in German (with an English translation), and involved non-physiological exposures to NMP (ip injection). However, it provides some very useful data for addressing the issue at hand. The exposure periods considered by the study authors included the following:

- (1) 1-day exposures to 129 or 166 mg/kg NMP on days 3, 7, 9, or 11 of gestation;
- (2) 5-day exposures to 74, 92, or 129 mg/kg-day NMP on days 7-11 of gestation; and
- (3) 14-day exposures to 14, 37, or 74 mg/kg-day NMP on days 1-14 of gestation.

The authors of this study assessed fetal resorptions in control and treated groups (11 treatment variations in total). Because this study included multiple durations and windows of exposure, these data permit an assessment of Haber's conjecture (equal values of *Dose x Time* produce equivalent responses). Schmidt et al. (1976) resorption data assessed in terms of *Dose x Time*ⁿ yield an optimized value for n of 0.31, as depicted in **Figure 3**.

Figure 3. Use of Fetal Resorption Data for Mice Exposed to NMP (Schmidt et al., 1976) to Assess the Relative Importance of Dose and Duration



Based upon the relationship defined for the relative importance of dose and time using NMP-specific data, the NMP dose for a single day exposure is predicted to be approximately 2.3-fold higher than that for a 15-day exposure to yield an equivalent rate of fetal resorptions. The value supported by these data is remarkably similar to the average suggested by van Raij et al. (2003) for chemicals as a group (2.3 vs. 2.1). *Based upon this consideration, USEPA's 15-day POD value of 214 mg/L should be adjusted to be 2.3-fold higher (492 mg/L) for a single day exposure. Similarly, the recommended 15-day POD value of 548 mg/L (see Comment #1) would correspond to a 1-day value of 1,260 mg/L.*

It should be noted that this evaluation for NMP assumes that a “day” is the appropriate time unit for scaling gestational exposures across species. To the extent that “fraction of gestation” serves as a more appropriate time unit for scaling, the recommendations in this comment may be viewed as conservative since a single day represents a much larger fraction of a rat's gestation period (1/20 days or 5%) than that of a human's gestation period (1/280 days or 0.4%).

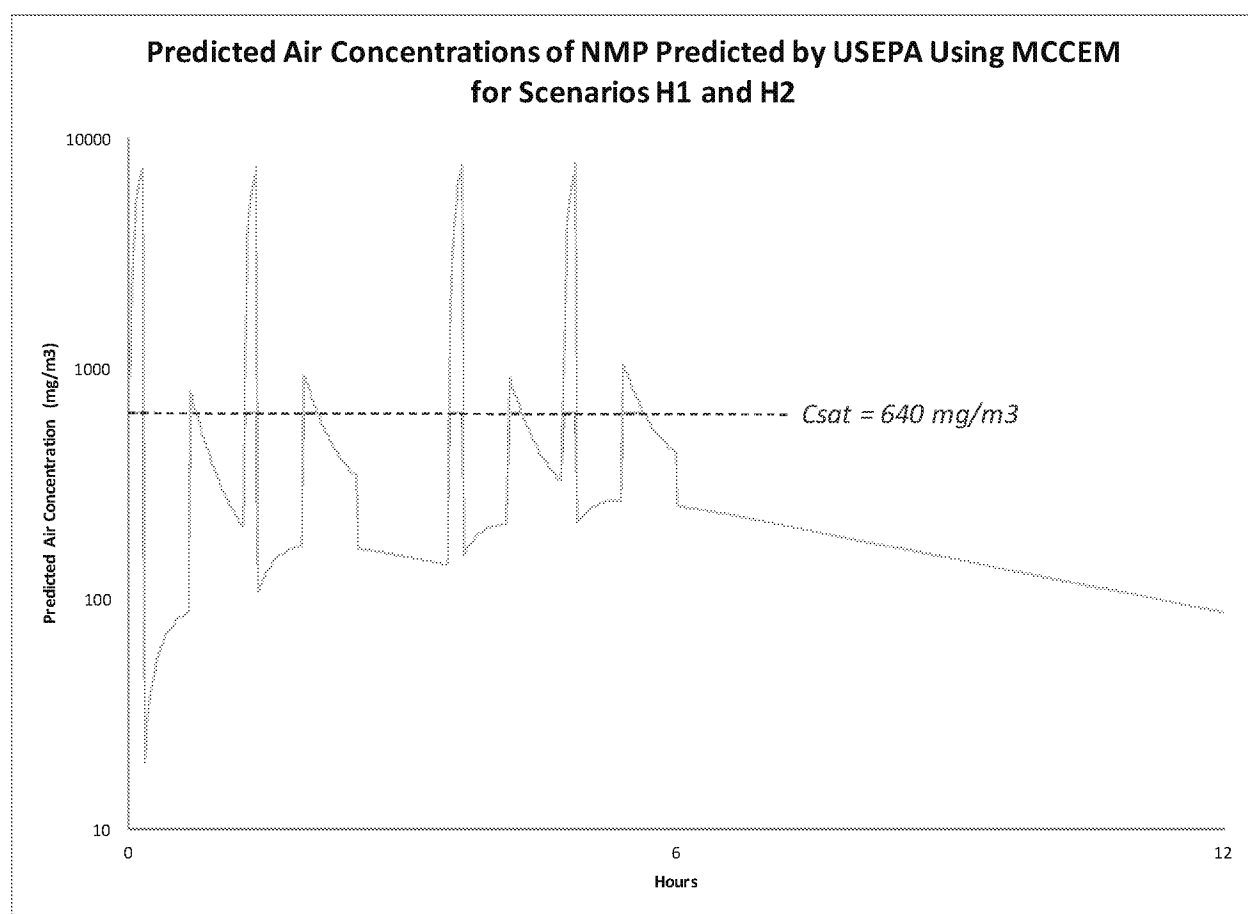
Comment #3: USEPA Appears To Have Omitted Including A Value For Csat In Its Modeling To Predict Indoor Air Concentrations, Resulting In An Overestimate Of Exposures To NMP

In USEPA's 2015 TSCA for NMP assessment (USEPA, 2015), modeled air concentrations for residential/consumer exposure scenarios were specifically limited not to exceed the concentration at which the air becomes saturated (Csat). Two values were considered for Csat in the 2015 assessment, 640 mg/m³ and 1,013 mg/m³. Inspection of the following support file for the 2016 supplemental report:

- 76_1_-_Appendix_B_SUPPL_Analysis_Consumer_NMP_paint_removal.xls

reveals modeled air concentrations as high as 7,771 mg/m³ for NMP, which suggests that Csat was not implemented by USEPA within the MCCEM software. Since these concentrations are used as input into the PBPK model, ignoring Csat has profound impact on predicted blood measurements for NPM. An assessment was conducted here for the 9 exposure scenarios (Scenarios E1 through H2) with inhalation exposures that exceed Csat (640 mg/m³ used here). For this assessment, all time points with air concentrations exceeding Csat were replaced with a value equivalent to Csat (i.e., exposures above this value were not permitted). An example air concentration profile for Scenario H2 is provided in **Figure 4**.

Figure 4. Example Time Course Profile Predicted for NMP by USEPA Using MCCEM (solid blue line = predicted air concentrations; dashed redline = Csat value for which predicted air concentrations should not exceed)



In this scenario (Bathtub, spray evaluation), USEPA predicted air concentration that exceed Csat 8 times within a 6-hour period. For our evaluation, we used the Csat-limited air concentrations for all 9 scenarios (E1-H2) as input into the PBPK model to predict the peak concentration of

NMP in maternal blood. A comparison of the predicted blood concentrations for the 9 scenarios is provided in **Table 1**.

Table 1. Impact of Including Csat (640 mg/m³) in Indoor Air Modeling on PBPK Predictions for Peak NMP in Blood (Cmax)

Exposure Scenario (no gloves)	Peak Concentration NMP in Blood (Cmax, mg/L)		% Change from Reported Value
	Csat Not Included as Reported in USEPA (2016)*	Csat of 640 mg/m ³ Included (estimated here)	
E1: Bathtub brush application	7.8	7.5	-4%
E2: Bathtub brush application	10.0	7.5	-25%
F1: Dining table/chairs spray application	14.7	9.8	-34%
F2: Dining table/chairs spray application	18.4	11.2	-39%
F3: Dining table/chairs spray application	14.2	9.7	-31%
G1: Floors spray application	26.2	11.2	-57%
G2: Floors spray application	33.6	15.3	-54%
H1: Bathtub spray application	25.3	7.2	-71%
H2: Bathtub spray application	38.6	11.4	-70%

*Note – We were unable to recreate USEPA predicted blood levels exactly, but were generally within 20% of the reported value for most scenarios. An explanation for this discrepancy is not apparent.

Based upon this assessment, we recommend that USEPA incorporate Csat in its air modeling for the supplemental report, as was performed in its 2015 assessment. In so doing PBPK model predictions for peak NMP in blood that are expected to be 4%-71% lower than presented in USEPA's supplemental report (USEPA, 2016).

Comment #4: Many of the Exposure Assumptions Used by USEPA are Expected to Overestimate Actual Exposures to NMP

Inspection of USEPA supplemental report reveals has relied upon assumptions that are more extreme than those assumed in USEPA's 2015 risk assessment. Because data regarding paint stripper use indicates that greater than 60% of paint stripper users do so either outside or in their garage (ABT, 1992), all the scenarios considered by USEPA reflect high-end exposures, and no estimate of exposure/hazard has been provided by USEPA for most-likely (i.e., central tendency) exposures to NMP. This oversight can result in a misperception of the likelihood of hazards associated with NMP use. As commented in the 2015 risk assessment, many of the exposures characterized by USEPA in the supplemental report generally ignore product labeling and/or MSDS handling instructions (e.g., avoid contact with skin, use in well ventilated area). As such, many of the evaluations assessed by USEPA go beyond "worst-case" analyses and instead fall under the general category of "product misuse". In particular, USEPA's bathtub scenarios are notable in that a very low ventilation rates are assumed (ACH = 0.18 hr⁻¹), despite

the fact that building codes generally require adequate ventilation (via window or exhaust fan) be present in bathrooms. While the need to provide a reasonable maximum exposure (RME) analysis is recognized, USEPA should present potential risks associated with product misuse (and abuse) separately from those associated with appropriate product use. In this way, risk management options for product misuse scenarios (e.g., labeling, user education/instruction) could be supported without resulting in the banning of products posing negligible risk under normal use conditions. *We recommend USEPA modify their assessment as follows: (1) For all exposure scenarios except for application to floors, a third option (i.e., in addition to the “Open Windows” and “Closed Windows” options provided) should be included to account for the most likely exposure scenarios involving moving items to be stripped outdoors/to garage prior to NMP application; (2) For the bathtub scenarios, two additional options should be included to account for higher air change rates associated “Window Open” and “Exhaust Fan On”; and finally (3) Exposure scenarios that are inconsistent with product labeling instructions should be labeled and presented separately as “Product Misuse Scenarios” so that risk management options for these scenarios can be addressed independently from “Product Use Scenarios”.*

Summary and Net Impact on MOE Values

Summit Toxicology has identified four areas in USEPA’s supplemental report for NMP (USEPA, 2016) that have contributed to an overestimation of potential hazard in its residential/consumer exposure scenarios. With respect to the toxicity assessment (**Comments 1 and 2**), the selection of an unusually low benchmark response rate, along with an assumption of equivalence for 1-day and 15-day exposures to NMP, the POD ($C_{max} = 214 \text{ mg/L}$ for NMP in blood) used by USEPA is lower than can be supported by NMP-specific data, and should be approximately 5.9-fold higher ($C_{max} = 1260 \text{ mg/L}$ for NMP in blood). With respect to the exposure assessment (**Comment 3**), USEPA’s apparent omission of C_{sat} in its air modeling has resulted in an overestimation of predicted exposures for scenarios E1-H2, and should be approximately 4%-71% lower. Note that air concentrations for all other scenarios (A1-D2), whose MOE values calculated >30 , are generally below a C_{sat} of 640 mg/m^3 , and therefore are generally unaffected by its omission. The combined impact of these three issues (note – the impact of Comment #4 has not been quantified) on resulting MOE values is summarized in **Table 2**.

Table 2. Net Impact of Three Issues on Estimated MOE Values

Exposure Scenario (no gloves)	MOE values as estimated by USEPA (USEPA, 2016)	MOE values as corrected here for issues in Comments 1-3 (see text)
E1: Bathtub brush application	28	170
E2: Bathtub brush application	22	170
F1: Dining table/chairs spray application	15	130
F2: Dining table/chairs spray application	12	110
F3: Dining table/chairs spray application	15	130
G1: Floors spray application	8.2	110
G2: Floors spray application	6.4	80
H1: Bathtub spray application	8.5	170
H2: Bathtub spray application	5.6	110

When the three issues identified above are appropriately addressed, MOE values for all 18 residential/consumer scenarios (A1-H2) are above a value of 30, indicating that the potential hazards associated these high-end exposure scenarios are negligible.



N-METHYLPYRROLIDONE PRODUCERS GROUP, INC.

2200 PENNSYLVANIA AVENUE, N.W., SUITE 100W, WASHINGTON, D.C. 20037 • (202) 557-3800 • FAX (202) 557-3836

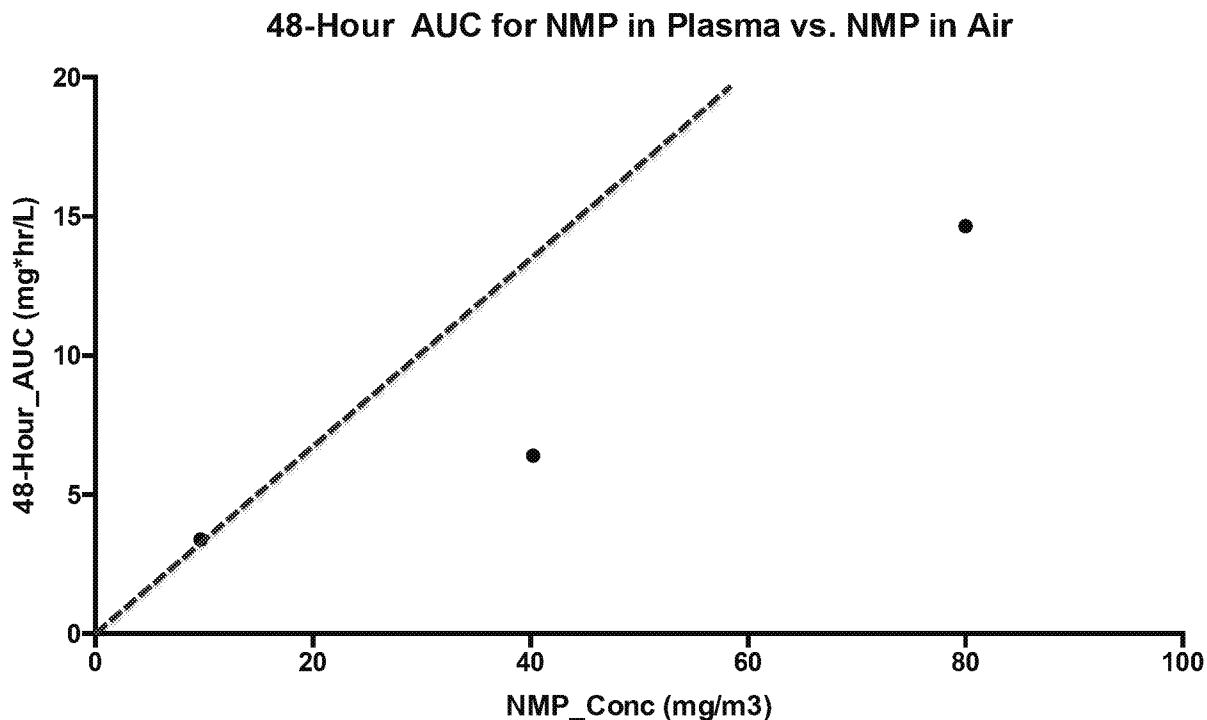
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NMP Producers Group Feedback on November 8, 2013, Peer Review Committee Discussion on Draft EPA Risk Assessment on NMP

The NMP Producers Group submits these additional comments in response to the November 8, 2013, peer review committee discussion on the draft N-methylpyrrolidone (NMP) risk assessment prepared by the U.S. Environmental Protection Agency (EPA).

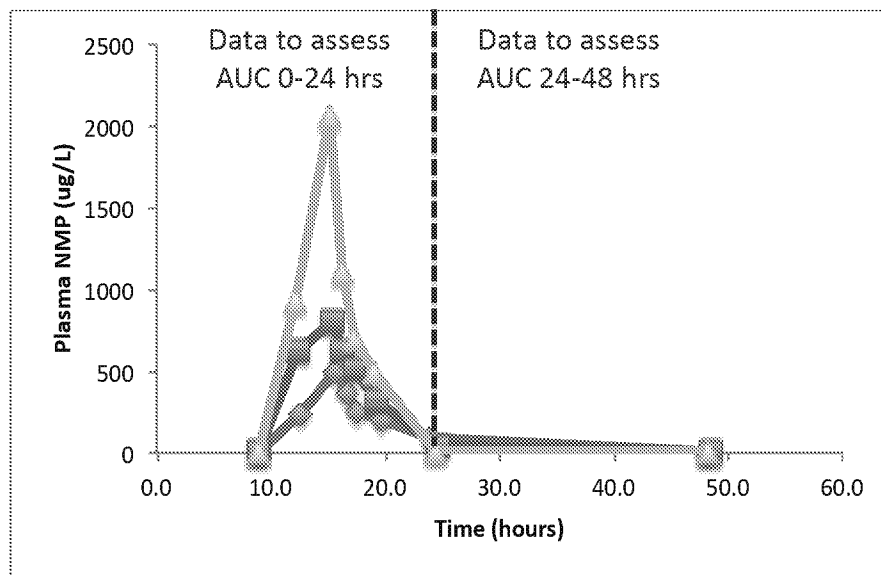
1. **The NMP Producers Group maintains that the plasma and urine data of Bader *et al.* (2007) and individual data provided in the unpublished report of Bader and van Thriel (2006) are consistent with linear toxicokinetics for NMP under the conditions of the study. There is, therefore, no reason to question or to make changes to the existing physiologically-based pharmacokinetic (PBPK) model for NMP.**
 - During the November 8, 2013, peer review meeting, there was a suggestion that the 0-48 h area under the curve (AUC) for NMP in plasma reported by Bader *et al.* (Bader *et al.*, 2007 and Bader and van Thriel, 2006) is nonlinear, indicating an induction of NMP metabolism at higher concentrations of NMP in air. This assertion, however, is based on uncertain, non-robust data. The panel member's comment is summarized in Figure 1, which asserts that when the 48 h plasma AUC values are normalized per unit NMP exposure, the value for the lowest test concentration (slope of the red dashed line in Figure 1) is higher than those calculated for the two higher test concentrations.

Figure 1



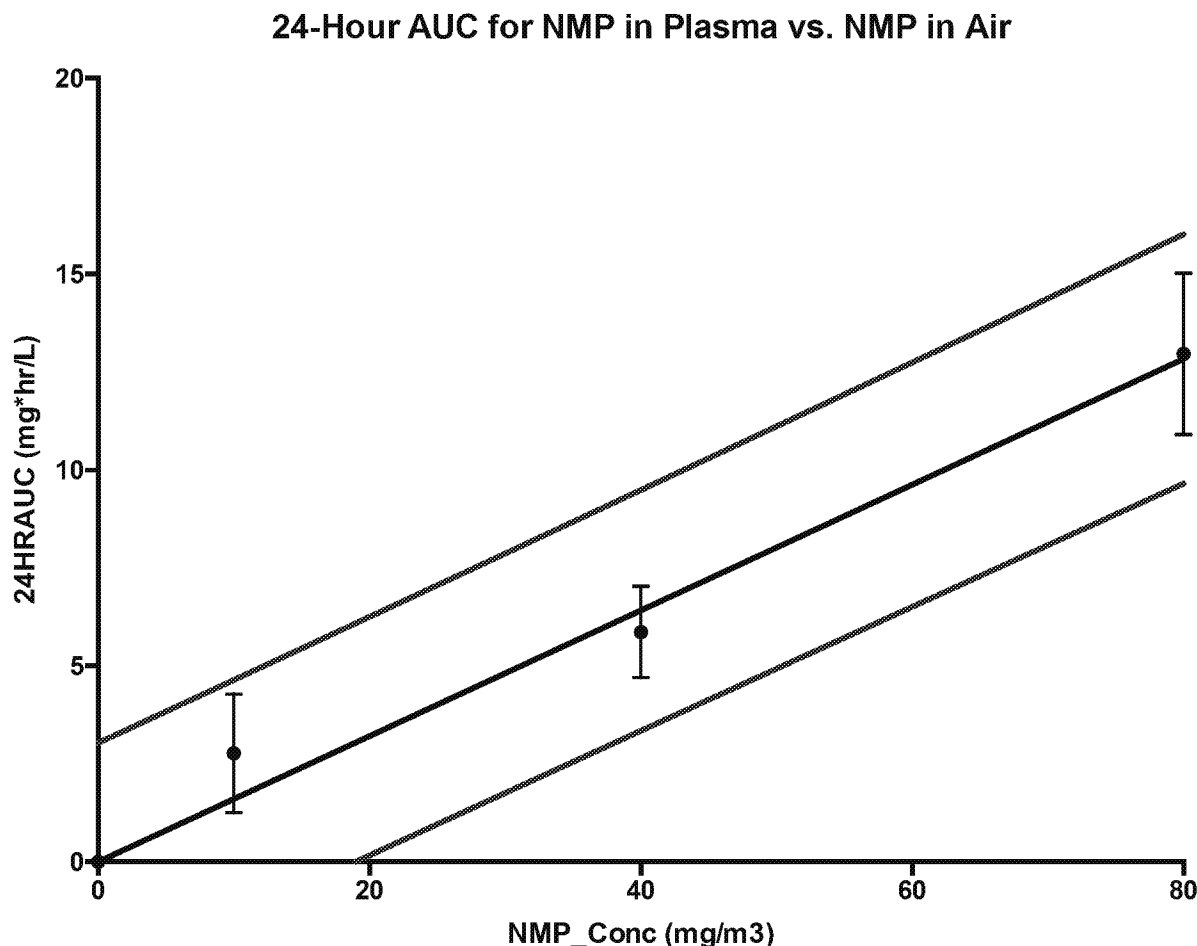
- To address this comment, a re-analysis of the Bader *et al.* (2007) data was performed. In examining the data, it is clear that there are important differences in the AUC values for 0-24 h and 24-48 h. For the 0-24 h timeframe, there are approximately 7 data points, which allow for AUC estimates with high confidence. Alternatively, the 24-48 h timeframe only has two data points, which make the AUC estimates less certain and unreliable. *See* Figure 2. For this reason, any analysis of potential nonlinear toxicokinetics should be focused on the 24 h AUC values.

Figure 2



- As shown below in Figure 3, the relationship between the 24 h AUC for NMP in plasma and external concentration (NMP in air, mg/m^3) appears linear between 0-80 mg/m^3 ($R^2 = 0.97$).
 - Although the data point for the lowest concentration (10 mg/m^3) falls slightly above this line, it falls well within the 95% prediction band defined by the data set (*i.e.*, 95% of data points are expected to fall between the red lines).

Figure 3



- In addition, the relationship between urinary metabolite excretion and external concentration (NMP in air, mg/m³) appears linear between 0-80 mg/m³ ($R^2 = 0.98-0.99$). As shown below in Figures 4 and 5, all data points are well within the 95% prediction bands defined by the data (95% of the data points are expected to fall between the red lines).
- If induction of metabolism were significant at the high concentrations, the data points for urinary metabolites would be expected to deviate upwards from linearity at the high concentrations. This is not seen for either 5-HNMP (5-hydroxy-N-methyl-2-pyrrolidone) or 2-HMSI (2-hydroxy-N-methylsuccinimide) in Figures 4 and 5.

Figure 4

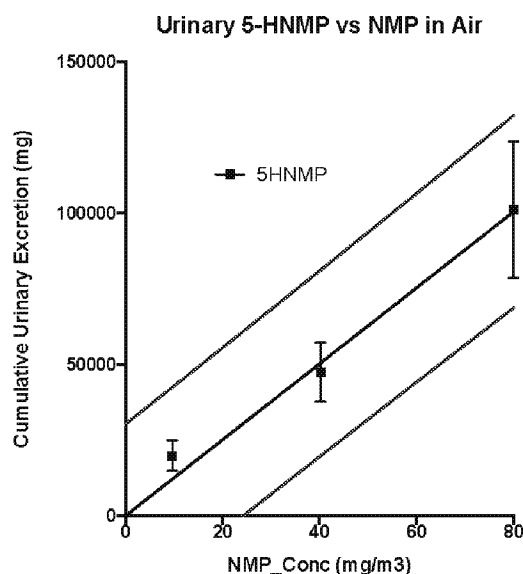
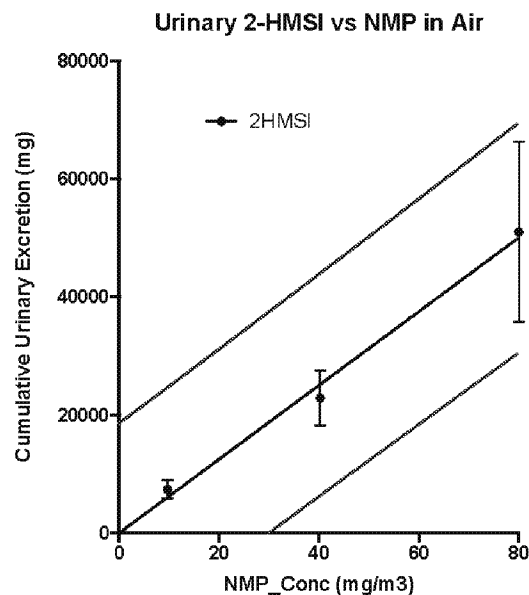


Figure 5



Recommendation: EPA should not revise the current PBPK model to include additional metabolic complexity. There does not appear to be any significant nonlinear behavior data in the toxicokinetic data collected by Bader *et al.* (2007) to support the view of metabolic differences.

2. EPA should not adopt any recommendation from the peer review committee that does not comport with current EPA guidance and policy.

- During the November 8, 2013, committee meeting, there was discussion about lowering the benchmark response (BMR) for fetal body weights to 1%.
- The proposal for a 1% BMR is based on an empirical correlation between body weights at birth and certain human health outcomes. However, this correlation is heavily influenced by the contributions of observations made well outside the normal birth weight range (*e.g.*, mean \pm 1SD) and is based on highly uncertain assumptions. Whether such a correlation is proof of a causal relationship has been discussed in the literature and requires consideration of the underlying biological mechanisms (Wilcox, 2001; Hernandez-Diaz et al., 2008). However, even if a causal relationship existed, it would not apply to NMP since the fetal/pup body weight decrements seen after maternally toxic exposures -- exposures that are unlikely in humans -- are small (*i.e.*, 4 - 7% of control), and less than 1 SD of the mean fetal/pup body weights of control rats. If EPA is interested in characterizing the relationship between NMP exposure and fetal/neonatal mortality, there are sufficient data in the NMP developmental and reproductive toxicity studies for this relationship to be addressed directly (*i.e.*,

without invoking an assumption of causation between fetal body weight and mortality).

- As stated in EPA's *Benchmark Dose Technical Guidance* (EPA, 2012a), "Typically, a BMR near the low end of the observable range is selected as the basis for obtaining BMDs [bench mark doses] and BMDLs [bench mark dose levels]" For the NMP data sets, selection of a BMR value of 1% would result in BMDL values that fall well below the range of observation defined by the data, and therefore its selection would be inconsistent with Agency guidelines.
- As shown in Table 2 of our supplemental comments dated October 16, 2013, a review of 25 recent Integrated Risk Information System (IRIS) assessments in which reference values were derived from continuous data reveals that a BMR of 1 SD was relied upon most frequently (13 of 25 cases); followed by a BMR of 10% (6 cases); a BMR of 5% (5 cases); and a BMR 2 SD in one case. There is no precedent for using a BMR of 1% for deriving a reference value on IRIS.
- In the recent IRIS review of tetrahydrofuran (EPA, 2012b), "the reviewers recommended using 1 SD below the control mean for pup body weight gain instead of a 5% decrease in body weight gain as the BMR to establish the POD, on the basis that a percentage reduction in body weight gain is an arbitrary choice compared with a measure of effect that considers the variation among animals." EPA concurred with this recommendation.
- If EPA selects a BMR other than 1 SD, it should follow its BMD guidance (EPA, 2012a) and indicate the Point of Departure (POD) for both the selected BMR and 1 SD.

Recommendation: The EPA risk assessment process should align with current EPA policies. If EPA opts to consider alternative approaches that do not comport to existing policies or practices, such as the adoption of a BMR of 1%, it should first solicit public review and comment on those policy changes before incorporating them into the NMP risk assessment.

3. EPA should not issue the NMP risk assessment using exposure values associated with scenarios of misuse.

- Because certain commercial and consumer products have inherent hazards, such as paint stripping products containing NMP, and because there is the possibility of exposure, the Federal Hazardous Substance Act (FHSA) requires these products to be labeled with information to alert consumers. The required information identifies the potential hazards and provides clear directions on what consumers must do to protect themselves.

- Ignoring or not following safety information is tantamount to misuse of the product.
- Conducting a risk assessment on misuse of a product is inappropriate.
- If it is to be assumed that consumers are not going to follow the safety instructions on a product, the purpose of the existing safety legislation is severely undermined.
- If manufacturers are going to be held accountable to communicate safe use and handling of their product, there should also be some accountability assigned to the downstream user.
- At a minimum, EPA should provide a risk estimate focused on the potential exposures resulting from the specified use of the product as communicated on the label, based on the requirements of the FHSA.
 - If EPA believes it is necessary to issue a risk estimate based on exposure values of consumers misusing the products and ignoring safety instructions, it should do so separately.

Recommendation: If EPA proceeds with using exposure values based on misuse of NMP containing products, it should include two separate sets of risk estimates -- one for consumers that follow safety directions (*i.e.*, labeled as “Product Use Scenarios”) and one for consumers that choose not to (*i.e.*, labeled “Product Misuse Scenarios”).

4. **EPA should rely on empirical data over hypothetical modeling predictions in order to decrease uncertainties and increase the relevance of conclusions to real world exposures.**

- Instead of modeling, EPA should consider the empirical data provided by its contractor in a study designed specifically to approximate a “worst-case” residential exposure to NMP (EPA, 1994). The chosen exposure conditions (*e.g.*, duration, amount of stripper used, stripping location, protective measure, ventilation) represented a combination of mean and upper-bound values (WESTAT, 1987; Abt, 1992) consistent with a reasonable maximum exposure (RME), which EPA (2001) defines as the highest exposure expected to occur at a site. The RME is intended to be a conservative estimate (*i.e.*, well above the average case) that is still within the range of possible exposures.
- The worst-case breathing zone concentration of NMP over two hours of paint stripping activity was 37-39 mg/m³ (9-10 ppm); the 8-h time weighted average (TWA) was 46-74 mg/m³ (11-18 ppm) for someone who remained in the

unventilated room (EPA, 1994). As expected by this EPA-approved protocol, these exposures were well above those observed under real world conditions, including exposures in poorly ventilated spaces, as exemplified below.

- Anundi *et al.* (2000) reported workers using NMP containing products to remove graffiti in poorly ventilated, confined spaces experienced a mean 8-h TWA concentration of 1.0 mg/m³ with a range of 0.03-4.5 mg/m³.
- Will and coworkers (2004) measured NMP exposures of employees at two small paint stripping shops during the application and removal of NMP containing stripper. During the duration for these activities (125-167 minutes), which approximates the median duration (120 minutes) for residential paint stripping activities identified by EPA (1994), the NMP concentrations measured with personal air samplers ranged between 1.0 – 3.8 mg/m³.
- Bader *et al.* (2006) studied NMP exposures to workers at a glue production facility where NMP was periodically used to clean large mixing vessels (500 L, which is slightly larger than a bath tub), drain valves, and tools. The 8-h TWA NMP levels in most work areas ranged between 0.2 and 3.0 mg/m³, while workers involved in manual cleaning experienced 8-h TWA concentrations of ≤15.5 mg/m³ and a single peak exposure of ≤ 85 mg/m³.
- An example of the limited value of the EPA model is its prediction that residents in the rest of the house (ROH) will be exposed to an NMP concentration of 40 mg/m³ (EPA, 2013a), a level that approximates the worst-case NMP exposure for individuals actually present in the poorly ventilated room from which the NMP emanates (EPA, 1994).

Recommendation: Worker and residential exposures should be based on empirical data. If modeling is used, it should consider the limited volatility of NMP and include realistic exposure variables so that the final predictions are consistent with real world observations.

5. EPA should revise the risk assessment to include the Saillenfait *et al.* (2002) as a key study for the selection of internal dose metrics. Given the availability of the PBPK model, EPA does not “need” a dermal study for the NMP risk assessment.

- As noted in the October 16, 2013, NMP supplemental comments and highlighted by several peer review committee members, the Becci *et al.* (1982) study has multiple weaknesses, particularly when compared to Saillenfait *et al.* (2002).

- The perception by one peer reviewer that the Becci study drawbacks might be ignored because the Agency “needed” a dermal study for its analysis is misguided given the EPA preference for use of the PBPK model and the internal dose metrics it provides.

It is not clear why EPA chose not to consider the Saillenfait *et al.* (2002) as a key study in the draft risk assessment. The reason may have been its belief (EPA, 2013b) that data on incomplete vertebral ossification, a key endpoint in the draft risk assessment, were not reported in the study. However, these data are reported (*see* Table 4; Saillenfait *et al.*, 2002). As noted in the October 16 NMP Producer Group’s supplemental comments, BMD results of incomplete vertebral ossification from the Saillenfait *et al.* (2002) and Becci *et al.* (1982) studies are inconsistent, further weakening the risk assessment value of Becci *et al.* (1982). [Note: In its BMD analysis of the incomplete vertebral ossification reported by Saillenfait *et al.* (2003), EPA also incorrectly used the litter sizes for external examinations instead of the litter sizes for skeletal examinations.]

- As detailed in the October 16, 2013, comments, significant effects to the dam following inhalation (Saillenfait *et al.*, 2003) occur at 10-fold lower internal doses than the internal doses producing the same effects in dams after gavage (Saillenfait *et al.*, 2002). This difference, combined with the other supporting information provided, indicates that the mode of action (MOA) for the toxicity caused by inhaling saturated NMP vapors (irritation induced maternal stress + subthreshold systematic toxicity) is different than that caused by NMP via other routes of exposure (systemic toxicity).

Recommendation: EPA should include both Saillenfait *et al.* studies (2002 and 2003) in its revised risk assessment and consider the decrements in fetal BW reported by Saillenfait as the most sensitive markers for repeated-dose effects from exposure to NMP. Because the MOA in the Saillenfait *et al.* (2003) inhalation study (*i.e.*, irritation induced maternal stress + subthreshold toxicity) is different than the MOA (*i.e.*, systemic toxicity) for other routes of exposure (Saillenfait *et al.*, 2002), route-specific BMDLs for the two different MOAs should be used to derive margins of exposure (MOE) for inhalation exposures (BMDL from Saillenfait *et al.*, 2003) versus other (oral, dermal) exposures (BMDL from Saillenfait *et al.*, 2002).

6. The NMP Producers Group recognizes that NMP is a data-rich chemical and not all NMP studies were considered in the draft risk assessment. As peer review committee members and stakeholders identify studies that may not have been included, EPA must carefully consider not only the identified studies, but other studies relevant to the area in question and whether those studies provide relevant information for human health risk assessment.

- For example, one peer review committee member suggested that EPA should include an analysis of the one-generation oral study of NMP in rats by Sitarek *et al.* (2012). If EPA accepts this suggestion, it must also consider results from

other related studies, including the more robust two-generation oral studies of NMP in rats performed by BASF (1999) and Huntingdon Life Science (1999).

- One peer review committee member suggested increasing the acceptable MOE from 30 due to the high (*i.e.*, 5-fold) variability in humans of an enzyme (CYP2E1) involved in the metabolism of NMP (Ligocka *et al.*, 2003). EPA should be aware, however, that the study authors concluded that while this isoform plays a partial role in the metabolism of NMP in rats, it plays a lesser role in humans. No data are provided to indicate that the overall metabolism of NMP in the human population is highly variable; therefore, an increase in the MOE is unwarranted.

Recommendation: If EPA decided to include new areas or endpoints for review in the risk assessment, all studies relevant to the area in question should be included to provide a balanced interpretation of the available data. Likewise, if new studies are considered, EPA should fully evaluate the potential role the data have in human health risk assessment.

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